# EXHIBIT 16

**IN THE UNITED STATES PATENT OFFICE**

Application Serial No. 09/465,338 Our Ref.: PT1817000

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| Applicant | : BIOVAIL LABORATORIES INCORPORATED | Agent: | Ivor M. Hughes, Suite 200, 175 Commerce Valley Drive West, Thornhill, Ontario Canada L3T 7P6 |
| Title | : CHRONOTHERAPEUTIC FORMULATIONS OF DILTIAZEM AND THE ADMINISTRATION THEREOF | | |
| Inventors | : Kenneth Stephen Albert<br>Paul José Maes | | |
| Examiner: | A. Pulliam | | |
| Group Art Unit: | 1615 | Due Date: February 4, 2004 | |



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**RESPONSE TO OFFICIAL ACTION**
**OF AUGUST 4, 2003**
**AMENDMENTS AND REMARKS**

February 3, 2004

The Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 South Clark Place
Customer Window, Mail Stop Patent Application
Crystal Plaza Two, Lobby, Room 1B03
Arlington, Virginia 22202
U.S.A.

Dear Sir:

INTRODUCTORY COMMENTS

In response to the outstanding Official Action dated August 4, 2003 and due for response November 4, 2003, Applicant encloses a Request for a three month extension of time with the fee for a large entity of $950.00 U.S. funds making this response due **February 4, 2004**. If there is any deficiency or surplusage of the fees enclosed for the Extension of Time, please obtain any such deficiency or credit the surplusage to Deposit Account 08-3255 and advise Applicants' Agent.

Please enter the following submissions:

AMENDMENTS TO THE CLAIMS

Claim 1 (currently amended): A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours the dosage comprising at least one bead comprising a core and at least one coating, the at least one bead containing from about 120 mg to about 540 mg of the form of Diltiazem, the Diltiazem in the core of the at least one bead associated with excipients, said at least one coating comprising at least one lubricant and/or at least one hydrophilic polymer and at least one water insoluble swellable polymer, said at least one water insoluble swellable polymer comprises a neutral copolymer, whereby the at least one coating permits hydration of the core by gastrointestinal fluids, the coated bead providing controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration of the preparation, the preparation being in a sustained-release dosage form in which the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the form of Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours.

Claim 2 (currently amended): A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours the dosage comprising at least one bead comprising a core and at least one coating, the at least one bead containing from about 120 mg to about 540 mg of the form of Diltiazem, the Diltiazem in the core of the at least one bead associated with excipients, said at least one coating comprising at least one lubricant and/or at least one hydrophilic polymer, and at least one water insoluble swellable polymer, said at least one water

insoluble swellable polymer comprises a neutral copolymer, whereby the at least one coating permits hydration of the core by gastrointestinal fluids, the coated bead providing controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation being in a sustained-release dosage form in which the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the form of Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;
(b) between about 16% and about 30% after 4 hours;
(c) between about 44% and about 62% after 8 hours;
(d) in excess of about 80% after 24 hours.

Claim 3 (previously amended): The preparation of claim 1 or 2 wherein the lubricant is selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative and/or the hydrophilic polymer is selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof.

Claim 4 (previously amended): The preparation of claim 2 wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

Claim 5 (previously amended): The preparation of claim 1, 2, 3 or 4 wherein the preparation is a diffusion controlled preparation.

Claim 6 (previously amended): The preparation of claim 1, 2, 3, or 4 wherein the preparation releases the form of Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

Claim 7 (previously amended): The preparation of claim 1, 2, 3, or 4 wherein the preparation is in capsule form.

Claim 8 (previously amended): The preparation of claim 1, 2, 3, or 4 wherein the preparation is in tablet form.

Claim 9 (previously amended): The preparation of claim 1, 2, 3, or 4 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

Claim 10 (previously amended): The preparation of claim 1, 2, 3 or 4 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the form of Diltiazem is mixed with the wetting agent.

Claim 11 (previously amended): The preparation of claim 1, 2, 3 or 4 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the form of Diltiazem is mixed with the wetting agent wherein the wetting agent assists to maintain the solubility of the form of Diltiazem in each bead, ensuring that the solubility of the form of Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

Claim 12 (previously amended): The preparation of claim 1, 2, 3 or 4 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

Claim 13 (previously amended): The preparation of claim 1, 2, 3 or 4 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the preparation comprises a

mixture of the form of Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer and the at least one water insoluble swellable polymer comprises a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

Claim 14 (previously amended): The preparation of claim 1, 2, 3 or 4 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the membrane comprises a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester and hydroxypropylmethylcellulose and the at least one water insoluble swellable polymer comprises a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester.

Claim 15 (previously amended): The preparation of claim 1, 2, 3 or 4 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the form of diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

Claim 16 (previously amended): The preparation of claim 9 wherein the form of Diltiazem is mixed with the wetting agent and the membrane comprises N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propenyl)oxy]-chloride ethanaminium polymer with ethyl-2-propenoate and methyl-2-methyl-2-propenoate, an acrylic polymer and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the form of diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

Claim 17 (previously amended): The preparation of claim 1, 2, 3, or 4 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or a pharmaceutically acceptable salt thereof associated with a dissolution agent (other than a wetting agent) to assist in the release of the form of Diltiazem from the preparation.

Claim 18 (previously amended): The preparation of claim 1, 2, 3 or 4 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with a dissolution agent (other than a wetting agent) to assist in the release of the form of Diltiazem from the preparation and wherein the dissolution agent is an organic acid selected from the group consisting of adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid which permits the form of diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into the higher pH regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

Claim 19 (currently amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning the preparation comprising a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours the dosage comprising at least one bead comprising a core and at least one coating, the at least one bead containing from about 120 mg to about 540 mg of the form of Diltiazem, the Diltiazem in the at least one bead associated in the core of each bead with excipients, said at least one coating comprising at least one lubricant and/or at least one hydrophilic polymer and at least one water insoluble swellable polymer, said at least one water insoluble swellable polymer comprises a neutral copolymer, whereby the at least one coating permits hydration of the core by gastrointestinal fluids, the at least one bead providing controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the form of Diltiazem is adapted to be released after administration over a prolonged period of time and being adapted to release the form of Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours

the method comprising administering to a patient in need thereof, the preparation in the evening.

Claim 20 (currently amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning, the preparation comprising a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours the dosage comprising at least one bead comprising a core and at least one coating, the at least one bead containing from about 120 mg to about 540 mg of the form of Diltiazem, the Diltiazem in the at least one bead associated in the core of each bead with excipients, said at least one coating comprising at least one lubricant and/or at least one hydrophilic polymer, and at least one water insoluble swellable polymer, said at least one water insoluble swellable polymer comprises a neutral copolymer, whereby the at least one coating permits hydration of the core by gastrointestinal fluids, the at least one bead providing controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the form of Diltiazem is adapted to be released after administration over a prolonged period of time and being adapted to release the form of Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:
(a) between about 4% and about 15% after 2 hours;
(b) between about 16% and about 30% after 4 hours;
(c) between about 44% and about 62% after 8 hours;
(d) in excess of about 80% after 24 hours

the method comprising administering to a patient in need thereof, the preparation in the evening.

Claim 21 (previously amended): A method of claim 19 or 20 wherein the lubricant is selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative and/or the hydrophilic polymer is selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof.

Claim 22 (previously amended): A method of claim 19 wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

Claim 23 (previously amended): A method of claim 20 wherein the preparation is a diffusion controlled preparation.

Claim 24 (previously amended): A method of claim 19, 20, 21, 22 or 23 wherein the preparation releases the form of Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

Claim 25 (previously amended): A method of claim 19, 20, 21, 22 or 23 wherein the preparation is in capsule form.

Claim 26 (previously amended): A method of claim 19, 20, 21, 22 or 23 wherein the preparation is in tablet form.

Claim 27 (previously amended): A method of claim 19, 20, 21, 22 or 23 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

Claim 28 (previously amended): A method of claim 19, 20, 21, 22 or 23 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the form of Diltiazem is mixed with the wetting agent.

Claim 29 (previously amended): A method of claim 19, 20, 21, 22 or 23 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane

and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the form of Diltiazem is mixed with the wetting agent wherein the wetting agent assists to maintain the solubility of the form of Diltiazem in each bead, ensuring that the solubility of the form of Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

Claim 30 (previously amended): A method of claim 19, 20, 21, 22 or 23 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

Claim 31 (previously amended): A method of claim 19, 20, 21, 22 or 23 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the preparation comprises a mixture of the form of Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

Claim 32 (previously amended): A method of claim 19, 20, 21, 22 or 23 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the water insoluble swellable polymer in the membrane comprises a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester and hydroxypropylmethylcellulose.

Claim 33 (currently amended): A method of claim 19, 20, 21, 22 or 23 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the

form of diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

Claim 34 (previously amended): A method of claim 19, 20, 21, 22 or 23 wherein the form of Diltiazem is mixed with the wetting agent and the membrane comprises N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propenyl)oxy]-chloride ethanaminium polymer with ethyl-2-propenoate and methyl-2-methyl-2-propenoate, an acrylic polymer and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the form of diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

Claim 35 (previously amended: A method of claim 19, 20, 21, 22 or 23 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or a pharmaceutically acceptable salt thereof associated with a dissolution agent (other than a wetting agent) to assist in the release of the form of Diltiazem from the preparation.

Claim 36 (previously amended): A method of claim 19, 20, 21, 22 or 23 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with a dissolution agent (other than a wetting agent) to assist in the release of the form of Diltiazem from the preparation and wherein the dissolution agent is an organic acid selected from the group consisting of adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid which permits the form of diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into the higher pH regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

Claim 37 (previously amended): The preparation of claim 1, 2, 3, or 4 wherein the preparation contains 120 mg of Diltiazem.

Claim 38 (previously amended): The preparation of claim 1, 2, 3, or 4 wherein the preparation contains 180 mg of Diltiazem.

Claim 39 (previously amended): The preparation of claim 1, 2, 3, or 4 wherein the preparation contains 240 mg of Diltiazem.

Claim 40 (previously amended): The preparation of claim 1, 2, 3, or 4 wherein the preparation contains 300 mg of Diltiazem.

Claim 41 (previously amended): The preparation of claim 1, 2, 3, or 4 wherein the preparation contains 360 mg of Diltiazem.

Claim 42 (previously amended): The preparation of claim 1, 2, 3, or 4 wherein the preparation contains 420 mg of Diltiazem.

Claim 43 (previously amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of claim 37, 38, 39, 40, 41 or 42 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 44 (currently amended): A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane comprising at least one lubricant and/or at least one hydrophilic polymer and at least one water insoluble swellable polymer which permits hydration of the core by gastrointestinal fluids, said at least one water

insoluble swellable polymer comprises a neutral copolymer, and wherein the wetting agent is selected from the group consisting of:

sugars;
saccharose, mannitol, sorbitol;
lecithins;
$C_{12}$ to $C_{20}$ fatty acid esters of saccarose,;
xylose esters or xylites;
polyoxyethylenic glycerrides;
esters of fatty acids and polyoxyethylene;
sorbitan fatty acid esters;
polyglycides-glycerides and polyglycides-alcohols esters and
Metal salts.

Claim 45 (previously amended): The preparation of claim 9 wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

Claim 46 (previously amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of claim 44 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 47 (previously amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of claim 3 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane and wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

Claim 48 (previously amended): A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about

120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane in which the core and membrane comprise:

| | | % W/W |
|---|---|---|
| (a) | Diltiazem hydrochloride | 69 - 73 |
| (b) | Microcrystalline cellulose | 8 - 9.5 |
| (c) | Povidone K30 | 1 - 2 |
| (d) | Sucrose stearate | 7 - 8 |
| (e) | Magnesium stearate NF | 0.5 - 2.5 |
| (f) | Talc USP | 0.5 - 5.0 |
| (g) | Titanium dioxide (USP) | 0.15 - 0.3 |
| (h) | Hydroxypropylmethylcellulose 2910 | 0.3 - 0.6 |
| (i) | Polysorbate 80 (tween) | 0.01 - 0.025 |
| (j) | Simeticone C emulsion USP (dry of 30%) | 0.01 - 0.015 |
| (k) | a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%) | 7 - 11 |
| | Purified water USP | 0 (used for mixing). |

Claim 49 (previously amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of claim 48 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 50 (previously amended): A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of at least on lubricant, and/or

(d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer; and

(e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants, which permits hydration of the core by gastrointestinal fluids.

Claim 51 (previously amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of claim 50 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 52 (previously amended): A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;

(b) between about 7% and about 45% after about 4 hours;

(c) between about 30% and about 68% after about 8 hours;

(d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of at least one lubricant, and/or

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer; and

(e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants, which permits hydration of the core by gastrointestinal fluids.

Claim 53 (previously amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of claim 52 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 54 (previously amended): The preparation of claim 9, 10, 11, 12, 13, 14, 15, 16, 44 or 45 wherein the preparation is a tablet and the tablet comprises microgranules

in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with excipients and adjuvants.

Claim 55 (previously amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of claim 54 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 56 (previously amended): A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of at least one lubricant, and/or

(d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer; and

(e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants, which permits hydration of the core by gastrointestinal fluids.

Claim 57 (original): The preparation of claim 56 wherein the microgranules are in capsule form.

Claim 58 (original): The preparation of claim 56 wherein the microgranules are in tablet form.

Claim 59 (previously amended): The preparation of claim 56, 57 or 58 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of at least one lubricant, and/or

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer; and

(e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants.

Claim 60 (previously amended): A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15

hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants wherein the core and membrane comprise:

| | | % W/W |
|---|---|---|
| (a) | Diltiazem hydrochloride | 69 - 73 |
| (b) | Microcrystalline cellulose (Avicel ph101) | 8 - 9.5 |
| (c) | Povidone K30 | 1 - 2 |
| (d) | Sucrose stearate (crodesta F150) | 7 - 8 |
| (e) | Magnesium stearate NF | 0.5 - 2.5 |
| (f) | Talc USP | 0.5 - 5.0 |
| (g) | Titanium dioxide (USP) | 0.15 - 0.3 |
| (h) | Hydroxypropylmethylcellulose 2910 | 0.3 - 0.6 |
| (i) | Polysorbate 80 (tween) | 0.01 - 0.025 |
| (j) | Simeticone C emulsion USP (dry of 30%) | 0.01 - 0.015 |
| (k) | a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%) | 7 - 11 |
| | Purified water USP | 0 (used for mixing). |

Claim 61 (previously amended): The preparation of claim 56, 58, 59 or 60 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with excipients and adjuvants.

Claim 62 (previously amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of claim 56 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 63 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises a form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

Claim 64 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

Claim 65 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises a form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

Claim 66 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises a form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

Claim 67 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises a form of Diltiazem or

pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

Claim 68 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

Claim 69 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

Claim 70 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

Claim 71 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

Claim 72 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a

central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

Claim 73 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

Claim 74 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

Claim 75 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

Claim 76 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

Claim 77 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

Claim 78 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble

polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

Claim 79 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose.

Claim 80 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose.

Claim 81 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the

membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose.

Claim 82 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose.

Claim 83 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

Claim 84 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a

diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

Claim 85 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

Claim 86 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof

associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

Claim 87 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 120 mg of Diltiazem.

Claim 88 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the

solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 120 mg of Diltiazem.

Claim 89 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 120 mg of Diltiazem.

Claim 90 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions

which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 120 mg of Diltiazem.

Claim 91 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 180 mg of Diltiazem.

Claim 92 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble

polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 180 mg of Diltiazem.

Claim 93 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the Diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 180 mg of Diltiazem.

Claim 94 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the

membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 180 mg of Diltiazem.

Claim 95 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 240 mg of Diltiazem.

Claim 96 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in

gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 240 mg of Diltiazem.

Claim 97 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 240 mg of Diltiazem.

Claim 98 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a

concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 240 mg of Diltiazem.

Claim 99 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 300 mg of Diltiazem.

Claim 100 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 300 mg of Diltiazem.

Claim 101 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 300 mg of Diltiazem.

Claim 102 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 300 mg of Diltiazem.

Claim 103 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 360 mg of Diltiazem.

Claim 104 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 360 mg of Diltiazem.

Claim 105 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each

microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 360 mg of Diltiazem.

Claim 106 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 360 mg of Diltiazem.

Claim 107 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or

pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 420 mg of Diltiazem..

Claim 108 (previously added): The preparation of claim 1, 2, 3 or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 420 mg of Diltiazem.

Claim 109 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting

agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 420 mg of Diltiazem.

Claim 110 (previously added): The preparation of claim 1, 2, 3 or 4 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 420 mg of Diltiazem.

REMARKS

Claims 1-110 remain in the Application. No new subject matter has been added.

Applicant would like to acknowledge the Examiner's decision to allow Claims 48, 49 and 60. Further to the extensive discussion the Examiner had with Marcelo Sarkis and after reviewing the Examiner's Office Action, Applicant would like to clarify a few points:

1) At page 5, lines 12 and 13, the Examiner indicated that Mr. Sarkis questioned the patentability of the method of use claims as amended. Applicant would like to clarify that Mr. Sarkis was not questioning the patentability of the method of use claims but was asking the Examiner's position in respect of the method of use claims. Applicant does not want the sentence to be misconstrued as a concession that the patentability of the method of use claims is in question by the Applicant or Applicants' agent. The question of patentability was not being conceded. Mr. Sarkis was only questioning the Examiner's position. Applicant respectfully requests the Examiner to acknowledge this point in her next communication.

2) The Examiner has indicated that Claims 1-110 are provisionally rejected under the judicially created Doctrine of Double-Patenting over Claims 1-66, 110, 112-119 and 122-132 of co-pending Application No. 09/567,451. Furthermore, the Examiner has indicated that this is a provisional double-patenting rejection since the purported conflicting claims have not yet been patented. Applicant respectfully submits that Applicant will undertake to file a terminal disclaimer upon receiving an allowance of all the pending claims in this case over the prior art without agreeing that a terminal disclaimer is required.

ANTICIPATION

The Examiner has rejected Claims 1-15, 17, 19-37, 39, 43, and 63-78 under 35 U.S.C. 102(b) as being anticipated by EPA 856313 (hereinafter "EPA '313"). The Examiner states that EPA '313 discloses a once daily product wherein the release rates overlap those claimed by Applicant. Applicant respectfully submits that all the independent claims as amended in the present application includes the limitation of a neutral copolymer as the at least one water insoluble swellable polymer. EPA '313 does not teach nor suggest the use of a neutral copolymer. The Examiner states that Claim 8 of EPA '313 broadly teaches the use of copolymers of acrylic and methacrylic esters, which would include the use of a neutral copolymer as the water insoluble polymer. However, Applicant respectfully submits that this teaching in EPA '313 does not include a neutral copolymer. All of the Eudragit-type polymeric materials taught in EPA '313 are charged polymers. Applicant has provided below a table of the Eudragit-type polymers and their corresponding charges. This information would have been known to the skilled artisan at the time of filing of the EPA '313 application.

| Name | Charge |
|---|---|
| Eudragit RL | Cationic [ammonium] |
| Eudragit RS | Cationic [ammonium] |
| Eudragit L | Anionic [Carboxyl] |
| Eudragit S | Anionic [Carboxyl] |
| Eudragit E | Cationic [Diethyl amino] |
| Eudragit RL 30D | Cationic [ammonium] |
| Eudragit L 30D | Anionic [Carboxyl] |
| Eudragit E 12.5 | Cationic [Diethyl amino] |
| Eudragit RL 12.5 | Cationic [ammonium] |
| Eudragit RS 12.5 | Cationic [ammonium] |

Given that all of the Eudragit type polymers taught in EPA '313 are charged, Applicant submits that the skilled artisan, having read EPA' 313 in its entirety would

not have deviated from the teachings of EPA '313 to use a neutral copolymer as there is no motivation provided by the teachings of EPA '313 to use a neutral copolymer.

The Examiner has recommended a side-by-side comparison of the EPA '313 formulation to that of Applicant's claimed formulation. Applicant has now compared pharmacokinetic parameters of the preparation as claimed in the instant application (currently marketed as Cardizem LA), which is limited to a neutral copolymer, to the product described in EPA '313 (see Tables 1 and 2 and Figures 1 and 2). EPA '313 is equivalent to US 5,002,776, which is listed in the FDA Orange Book for Cardizem CD. The pharmacokinetic data for Cardizem CD has been published in Thiffault et al. (previously submitted to the Examiner - should the Examiner require a copy of this reference, please advise):

| Table 1 | | | | |
|---|---|---|---|---|
| Parameters | Cardizem LA 360 mg | | Cardizem CD 240 mg[a] | |
| | Day | Night | Day | Night |
| $AUC_{0-\tau}$ | 3691 ± 1449 | 4251 ± 1219 | 2008 ± 814 | 1754 ± 715 |
| $C_{max}$ | 274.5 ± 149.0 | 290.9 ± 94.0 | 137.7 ± 48.6 | 127.6 ± 47.8 |
| Plasma Fluctuation | 118.9 ± 70.8 | 93.6 ± 29.5 | 112.5 ± 25.5 | 125.8 ± 31.2 |

a – data based on Thiffault article
$AUC_{0-\tau}$ = Steady-state area under the curve, $\tau$ = dosing interval = 24 hours

To normalize for the differences in dosage strength of the two diltiazem preparations, the above data is presented below in Table 2 as a Night/Day ratio:

**Table 2**

| Parameters | Night/Day Ratio | |
|---|---|---|
| | Cardizem LA | Cardizem CD |
| AUC | 1.15 | 0.874 |
| $C_{max}$ | 1.06 | 0.927 |
| Plasma Fluctuation | 0.787 | 1.12 |

Table 1 shows the raw data for the various pertinent pharmacokinetic parameters. When the data in Table 1 is converted to Night/Day ratios of the pharmacokinetic parameters it is quite clear that the pharmacokinetics of LA is better than that of CD (Table 2). The LA formulation provides for a much higher bioavailability (both AUC and $C_{max}$ are > than 1) and lower plasma fluctuation (< 1) during the night than CD.

Figure 1: Mean Steady-State Diltiazem Concentrations Following Administration of Cardizem LA 360 mg

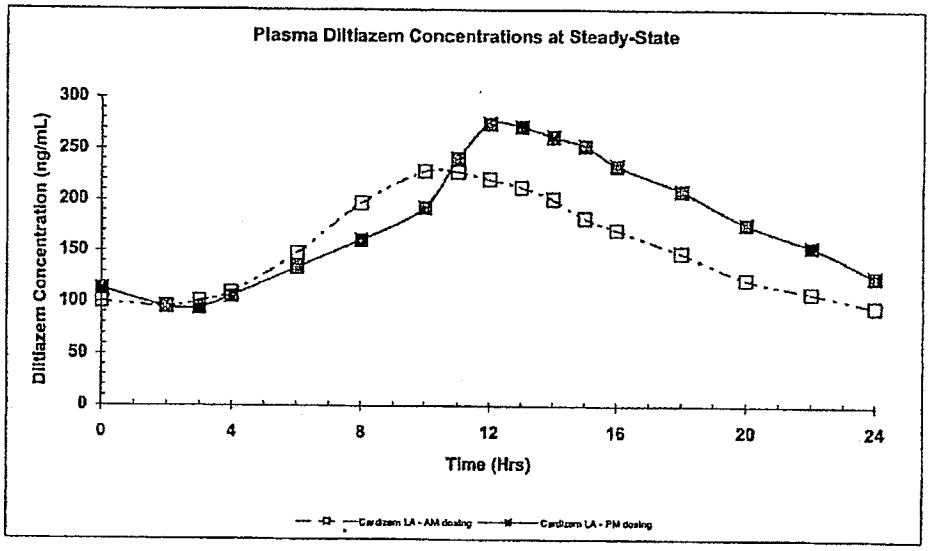
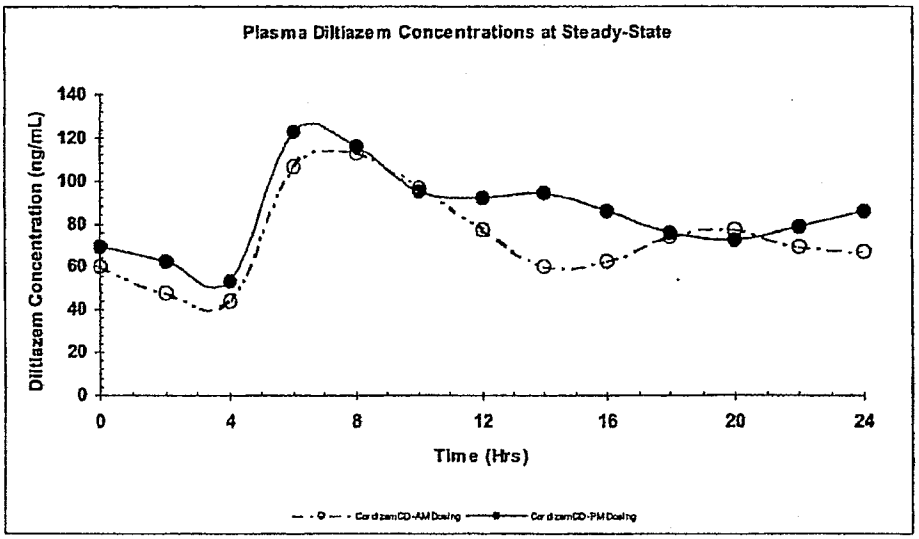


Figure 2: Mean Steady-State Diltiazem Concentrations Following Administration of Cardizem CD 240 mg




LA-PM vs. AM DOSING

Figure 1 together with Tables 1 and 2 demonstrate that:

1. When dosed in the evening, plasma diltiazem concentrations begins to rise at about 4 hrs after administration and peaks at about 11 hrs. Keeping in mind the fact that epidemiological studies have shown that the greatest incidence of heart problems and sudden cardiac death occur during the early morning waking hours when blood pressure is rising in response to the natural circadian rhythm, administering LA around 8-10 pm would result in diltiazem levels peaking during the critical early morning waking hours when the drug would be needed most,
2. A higher $C_{max}$ is reached when dosed in the evening (see also Tables 1 and 2),
3. The bioavailability of diltiazem is higher when LA is dosed in the evening (see Tables 1 and 2, AUC Night/Day ratio >1). The higher

bioavailability of diltiazem from the LA formulation translates to higher plasma diltiazem concentrations, and

4. LA exhibits a lower plasma fluctuation when compared to CD (see Table 2).

**CD PM vs. AM DOSING**

Figure 2 together with Tables 1 and 2 show that:

1. CD when dosed at night begins to increase around 4 hrs after administration and peaks about 6 hrs after administration. Thus, dosing CD around 8-10 pm would result in diltiazem levels peaking much too early (around 2-4 am),
2. A lower $C_{max}$ is reached when dosed in the evening compared to LA (almost half of LA, see Figure 2 and Tables 1 and 2, $C_{max}$ Night/Day ratio is < 1),
3. A lower bioavailability is achieved when dosing in the evening compared to LA (see Tables 1 and 2, AUC Night/Day ratio is < 1), CD exhibits much higher plasma fluctuation and hence more adverse effects compared to LA (see Table 2).

The above data clearly show the unexpected results obtained by the instantly claimed invention, which comprises the use of a neutral copolymer, compared to the product described by EPA '313, which teaches the use of charged copolymers of acrylic and methacrylic acid ester polymers and neither teaches nor suggests the use of a neutral copolymer. Further, EPA '313 neither teaches nor suggests the night-time effect of administering its product on the bioavailability of diltiazem. This effect would not be inherent to the EPA '313 product as the pharmacokinetics of the product disclosed in EPA '313 is significantly different from the product as claimed in the instant invention as established by the data above. All of the unexpected

novel features of the instantly claimed invention result in a true chronotherapeutic formulation. Therefore, Applicants' invention clearly exhibits unexpected results.

Applicant respectfully submits that the Examiner has not pointed to any facts or evidence establishing that any acrylic acid and methacrylic ester will necessarily result in the product of the instantly claimed invention. Indeed, the data provided above, clearly demonstrates that not every acrylic and methacrylic ester will function to provide the beneficial release profile for diltiazem of the instantly claimed invention. Accordingly, Applicant respectfully submits that the teaching in EPA '313 of the use of "copolymer of acrylic acid and methacrylic esters" is not broad, is limited to copolymers of acrylic and methacrylic acid which are charged, and certainly does not include the use of a neutral copolymer.

The Examiner refers to the teaching of claim 8 of EPA '313. It is undeniable, however, that a "neutral copolymer" is not explicitly taught or suggested in EPA '313. Applicant respectfully submits, however, that the Examiner has construed the term "copolymer of acrylic and methacrylic ester" as inherently including a "neutral copolymer".

A fundamental rule of claim construction is that terms in a patent document are construed with the meaning with which they are presented in the patent document. Bell Atl. Network Servs., Inc. v. Covad Communications Group, Inc., 262 F.3d 1258, 1267-68 (Fed. Cir. 2001); Multiform Desiccants, Inc. v. Medzam, Ltd., 133 F.3d 1473, 1477 (Fed. Cir. 1998). Thus claims must be construed so as to be consistent with the specification, of which they are a part. Gen. Am. Transp. Corp. v. Cryo-Trans. Inc., 93 F.3d 766, 770 (Fed. Cir. 1996); Slimfold Mfg. Co. v. Kinkead Indus. Inc., 810 F.2d 1113, 1117 (Fed. Cir. 1987). In order to establish that a particular element is inherently disclosed by a reference, it must be established that the descriptive matter missing from the reference is necessarily present in the reference's disclosure, and

that persons of ordinary skill in the art would recognize the presence of that element. Id. at 745, 49 USPQ2d at 1950-51, citing Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Inherency cannot, in law, be established by probabilities or possibilities. The fact that a specific result might occur from a certain set of circumstances is insufficient to establish inherency. Robertson, 169 F.3d at 745, 49 USPQ2d at 1951, citing Continental Can, 948 F.2d at 1269, 20 USPQ2d at 1749, citing In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

In this instance, Applicant respectfully submits that the Examiner has not pointed to any facts or evidence establishing that any acrylic and methacrylic acid ester will necessarily result in the product of the instantly claimed invention. If EPA '313 meant to include "neutral copolymers" in its preparation, then substituting a charged copolymer of acrylic and methacrylic acid ester with a neutral copolymer would result in a substantially similar release profile of the diltiazem regardless of whether a neutral or charged copolymer is used to make the chronotherapeutic diltiazem preparations. However, the data presented above clearly demonstrates this not to be the case. The release profiles obtained when using a neutral copolymer, as in the instantly claimed application, and that obtained when using a charged copolymer are significantly different and clearly demonstrates that not every acrylic and methacrylic ester will function to provide the beneficial release profile for diltiazem of the instantly claimed invention. Therefore, Applicant respectfully submits that the teaching in EPA '313 of the use of "copolymer of acrylic acid and methacrylic esters" is limited to the teaching of charged copolymers of acrylic and methacrylic acid esters only, is not broad and certainly does not include the use of a neutral copolymer.

Applicant respectfully submits, the claims of the instant application are not anticipated by EP' 313.

Applicant respectfully submits that the Examiner must read EPA '313 without 20/20 hindsight. At the time of filing and the publication of EP '313, Applicant respectfully submits that "neutral copolymers", in one instance a neutral copolymer, of acrylic acid and methacrylic esters were known and available. However, it is clear to one skilled in the art that from reading EPA '313 in respect of all references to the copolymers therein, such person would conclude that all the polymers listed in EPA '313 include the charged forms available at that time except neutral copolymers. See at page 4, lines 41-42, 53-54; page 5, lines 4-18, 52-53; and page 6, lines 1-7 of EPA '313. The table of Eudragit-type polymers and their charges provided above in this response listing the polymers found in EPA '313 with their charge support same.

> "Rejection for anticipation or lack of novelty requires, as the first step in the inquiry, that all the elements of the claimed invention be described in a single reference."

In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990), citing Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

The Examiner has not established that EPA '313 anticipates the claims in this application. The claims of the present invention require the at least one coating to have a neutral copolymer. EPA '313 discloses copolymers that are either anionic or cationic in nature, none more. The Examiner's statement of rejection with respect to EPA '313, Applicant respectfully submits fails to address the limitation in the claims of the at least one coating comprising a neutral copolymer.

Thus, Applicant respectfully submits, claims 1-15, 17, 19-37, 39, 43 and 63-78 are not anticipated by EPA '313. Reconsideration of the claims is respectfully requested.

OBVIOUSNESS – EPA ' 313

Claims 1-47, 50-59 and 61-110 of the instant invention have been rejected as being obvious in view of EPA 0 856 313 to Geoghegan *et al.* (EPA '313).

It is the Examiner's view that the skilled artisan, after having read EPA '313, would have been motivated to arrive at the instantly claimed invention through minimal experimentation, absent the presentation of some unexpected results by the Applicant. The Examiner has taken the position that the limitations of the instantly claimed invention are taught by EPA '313. In particular, it is the Examiner's opinion that the formulation disclosed in EPA '313 teaches a varied range of the amount of active ingredient, as well as the presence of additional additives, such as lubricants. The Examiner has also taken the position that the formulation disclosed in EPA '313 also releases the drug at the same rate as that claimed by Applicant. Therefore, it is the Examiner's position that these limitations do not render any unexpected results. It is the position of the Examiner that these are limitations, which would be routinely determined by one of ordinary skill through minimal experimentation, as being suitable, absent the presentation of some unexpected results.

Furthermore, it is the position of the Examiner that EPA '313 teaches the generic concept of the invention, as well as the suggestion to manipulate the formulation to result in varying dissolution rates and Cmax values. The Examiner further states that one of ordinary skill in the art would have been motivated to manipulate the formulation based on the specifics of the desired formulation. The expected result would be a successful pharmaceutical formulation. Therefore, this invention as a whole would have been, to the Examiner, *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant submits that the copolymer of acrylic and methacrylic ester taught in claims 8 and 10 of EPA '313 does not include a neutral copolymer. All of the

Eudragit type polymeric materials taught in EPA '313 are charged polymers as already shown in the table above.

Applicant respectfully traverses the Examiner's rejection and requests that the Examiner refer to the test results of Table 1, Table 2, Figure 1 and Figure 2, as well as the summary of the test results provided above in respect of a comparison between Applicant's invention and that of EPA '313. The Examiner will clearly see that there was no motivation in EPA '313 as there was no appreciation of the problem, which is overcome with Applicant's invention, namely a true chronotherapeutic formulation.

Once again, the data provided above clearly show the unexpected results obtained by the instantly claimed invention, which comprises the use of a neutral copolymer, compared to the product described by EPA '313, which teaches the use of charged copolymers of acrylic and methacrylic acid ester polymers and neither teaches nor suggests the use of a neutral copolymer. EPA '313 also does not teach or suggest the night-time effect of administering its product on the bioavailability of diltiazem. Further, this effect would not be inherent to the EPA '313 product as the pharmacokinetics of the product disclosed in EPA '313 is significantly different from the product as claimed in the instant invention as established by the data above. All of the unexpected novel features of the instantly claimed invention result in a true chronotherapeutic formulation. Therefore, as already mentioned above, Applicants' invention clearly exhibits unexpected results.

Thus, EPA '313 does not render Applicant's invention obvious. Reconsideration is respectfully requested.

OBVIOUSNESS – WO '093

The Examiner has also rejected Claims 1-47, 50-59, and 61 and 62 under 35 U.S.C. 103(a) as being unpatentable over WO 93/00093 (hereinafter "WO '093"). The

Examiner states that WO '093 discloses an extended release galenical form of Diltiazem or a pharmaceutically acceptable salt, with a wetting agent, coated with a microporous membrane comprising at least a water soluble polymer and a pharmaceutically acceptable adjuvant. The Examiner further states that WO '093 teaches that the composition comprises beads containing between 120 and 480 mg of the active ingredient, with the wetting agent, and the beads are coated with the microporous membrane (p. 19, claim 1). It is the Examiner's position that WO '093 further teaches that the water soluble polymer or copolymer can include HPMC and Eudragit (p. 8, l. 21-28), and that WO '093 teaches that the following ingredients are included in the formulation: wetting agents such as fatty acid esters of saccharose (2-20%), microcrystalline cellulose (5-25%), polyvinylpurrolidone (1-15%), titanium oxide, surfactants such as tween, antifoaming agents, magnesium stearate, and talc (see pages 8-10).

Although the Examiner takes the position that WO '093 teaches a formulation for once daily administration, WO '093 does not teach that the formulation is suitable for evening dosing as will be clearly seen in the data provided below. The Examiner has conceded that WO '093 does not teach the rates of release as claimed by Applicants and neither is there i) a discussion of the rates of release after eight hours or ii) specific amounts of the ingredients.

The Examiner further states that it is her position that the specific amounts of ingredients which are not disclosed in WO '093 are limitations which would be routinely determined by one of ordinary skill in art through minimal experimentation, absent the presentation of some unexpected results. Applicant respectfully submits that this is not the case. Specifically, in WO '093 there was no appreciation of a chronotherapeutic formulation as such. There was no appreciation of the problem associated with the current Diltiazem formulations available and the solution, namely a true chronotherapeutic formulation. In determining obviousness,

Applicant respectfully submits, one needs to recognize the problem, see, for example, *Monarch Knitting Machine Corporation v. Solzer Morat GmbH*, 45 USPQ 2d (1977), 1981-1982 (Fed. Cir. 1998)

> "where the District Court's formulation of the problem confronting the '053 inventors presumes the solution to the problem - modification of the stem segment. Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness. See, EG In re Antal, 58 CCPA·1382 444 F.2d 1168, 1171-72, 170 USPQ, 285, 287-88 (CCPA 1971)."

Therefore, again, Applicant respectfully submits WO '093 does not render obvious Applicant's invention. This is clearly shown in the data below where pharmacokinetic parameters of the preparation as claimed in the instant application currently marketed as Cardizem LA, which is limited to a neutral copolymer to the product described in WO '093 (see Tables 3 and 4 and Figures 1 and 3). WO '093 is equivalent to US 5,529,791, which is listed in the FDA Orange Book for Tiazac. Tiazac is not a chronotherapeutic product as clearly spelled out in Figure 8 of Applicant's application.

**Table 3**

| Parameters | Cardizem LA 360 mg | | Tiazac 360 mg[b] | |
|---|---|---|---|---|
| | Day | Night | Day | Night |
| $AUC_{0-\tau}$ | 3691 ± 1449 | 4251 ± 1219 | 2870 ± 1005 | 2754 ± 810 |
| $C_{max}$ | 274.5 ± 149.0 | 290.9 ± 94.0 | 243.2 ± 79.0 | 200.3 ± 59.1 |
| Plasma Fluctuation | 118.9 ± 70.8 | 93.6 ± 29.5 | 171.4 ± 43.8 | 144.8 ± 26.7 |

b – Data based on Bioclin Research Laboratories Analytical Report. Report is available should the Examiner request it.

$AUC_{0-\tau}$ = Steady-state area under the curve, $\tau$ = dosing interval = 24 hours

Table 4 below provides night/day ratio

| Table 4 | | |
|---|---|---|
| Parameters | Night/Day Ratio | |
| | Cardizem LA | Tiazac |
| AUC | 1.15 | 0.960 |
| $C_{max}$ | 1.06 | 0.824 |
| Plasma Fluctuation | 0.787 | 0.845 |

Table 3 shows the raw data for the various pertinent pharmacokinetic parameters. When the data in Table 3 is converted to night/day ratios of the pharmacokinetic parameters, it is quite clear that the pharmacokinetics of LA is better than that of Tiazac (Table 4). The LA formulation provides for a much higher bioavailability, both area under the curve and Cmax are greater than 1 and lower plasma fluctuation during the night than Tiazac.

For ease of reference and comparison, Figure 1 is re-produced below:

Figure 1: Mean Steady-State Diltiazem Concentrations Following Administration of Cardizem LA 360 mg

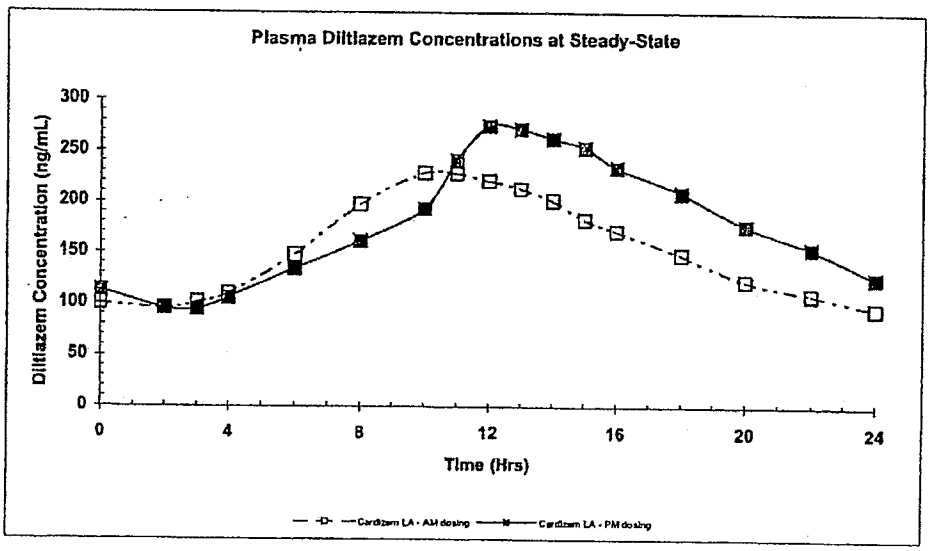
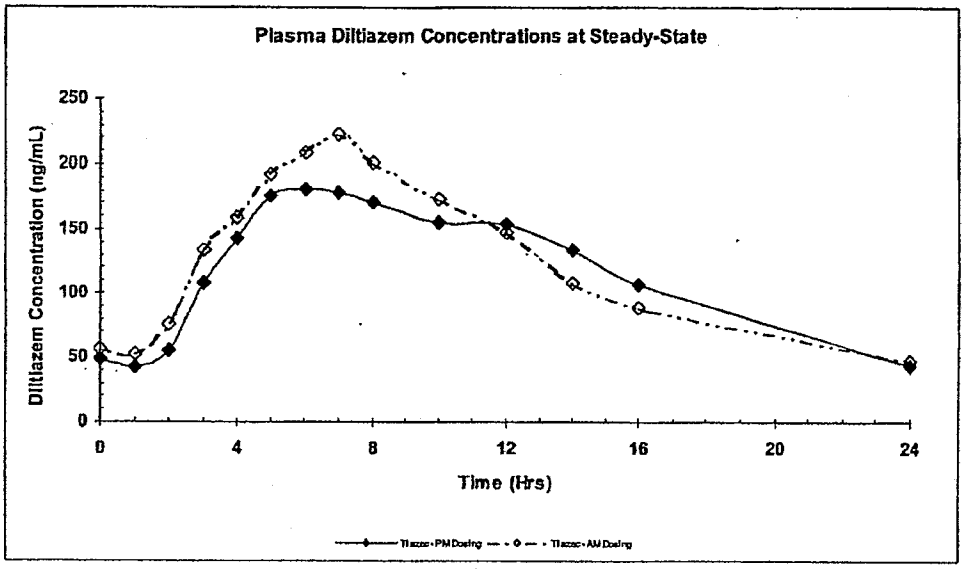


Figure 3: Mean Steady-State Diltiazem Concentrations Following Administration of Tiazac 360 mg




LA-PM vs. AM DOSING

Figure 1 together with Tables 3 and 4 demonstrate that:

1. When dosed in the evening, plasma diltiazem concentrations begins to rise at about 4 hrs after administration and peaks at about 11 hrs. Keeping in mind the fact that epidemiological studies have shown that the greatest incidence of heart problems and sudden cardiac death occur during the early morning waking hours when blood pressure is rising in response to the natural circadian rhythm, administering LA around 8-10 pm would result in diltiazem levels peaking during the critical early morning waking hours when the drug would be needed most,
2. A higher $C_{max}$ is reached when dosed in the evening (see also Tables 3 and 4),
3. The bioavailability of diltiazem is higher when LA is dosed in the evening (see Tables 3 and 4, AUC Night/Day ratio >1). The higher

bioavailability of diltiazem from the LA formulation translates to higher plasma diltiazem concentrations, and

4. LA exhibits a lower plasma fluctuation when compared to Tiazac (see Table 4).

**TIAZAC PM vs. AM DOSING**

Figure 3 together with Tables 3 and 4 show that:

1. Tiazac when dosed at night begins to increase around 2 hrs after administration and peaks at about 6 hrs after administration. Thus, dosing Tiazac around 8-10 pm would result in diltiazem levels peaking much too early (around 2-4 am),
2. A lower Cmax is reached when dosed in the evening compared to LA (see Figure 3 and Tables 3 and 4, Cmax Night/Day ratio is <1),
3. A lower bioavailability is achieved when dosed in the evening compared to LA (see Tables 3 and 4, AUC Night/Day ratio is <1),
4. Tiazac exhibits a higher plasma fluctuation and hence more adverse effects compared to LA (see Table 4).

The above data clearly shows the unexpected results obtained by the instantly claimed invention, which comprises the use of a neutral copolymer compared to the product described by WO '093. WO '093 does not teach or suggest a night time effect of administering its product on the bioavailability of diltiazem. Further, this effect would not be inherent to the WO '093 product as the pharmacokinetics of the product disclosed in WO '093 is significantly different from the product as claimed in the instant invention as established by the data above. All of the unexpected novel features of the instantly claimed invention result in the true chronotherapeutic formulation. Therefore, Applicant's invention clearly exhibits unexpected results. Furthermore, the above comparison, Applicant respectfully submits, addresses the Examiner's concern that the previous data submitted regarding Tiazac was

concerning a 240 mg formulation and the data regarding Applicant's claimed formulation was based on a 300 mg capsule. Now, the comparison to Tiazac, as well as to the Applicant's formulation, are now based on the same dosage amount, thus satisfying the Examiner's request.

Given the facts provided above, Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case for obviousness in view of EPA '313 and in view of WO '093. Again, the Applicant refers the Examiner to the data presented above showing the unexpected results obtained when a neutral copolymer is used.

Applicant respectfully reminds the Examiner that the criteria for obviousness determinations are well established in US Patent Law and have been set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). To establish obviousness based on a combination of the elements disclosed in the prior art there must be some motivation suggested in their teaching of the desirability of making the specific combination that was made by the Applicant. See In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000), citing In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635; 1637 (Fed. Cir. 1998) and In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

While the Examiner asserts that "One of ordinary skill in the art would have been motivated to manipulate the formulation based on the specifics of the desired formulation", the Examiner has not provided any analysis regarding how any one of the references should be modified to arrive at the claimed invention. Rather, the Examiner provides the conclusory statement that it would have been obvious to one of ordinary skill in the art at the time of the invention to create a controlled release formulation of diltiazem based on the teachings of EPA '313 or WO '093 with the reasonable expectation of producing a composition that would exhibit Applicants'

results which the Examiner states are not unexpected. As the Examiner has not, within a degree of specificity pointed to the relevant portion of the cited references which would have led the artisan of ordinary skill to arrive at Applicants' invention as claimed, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness.

The Examiner is also reminded of the decision of the BPAI Appeal No. 2001-1779, Application No. 09/398,898 where the Board concluded as Applicant has submitted above.

In view of the forgoing, Applicant submits that the claims are in condition for allowance and early reconsideration of the present application is respectfully requested subject to the judicially created double-patenting obviousness rejection.

If the Examiner has any questions, she is respectfully requested to contact Applicants' Agents, Ivor M. Hughes or Marcelo K. Sarkis at (905) 771-6414 collect at her convenience.

Respectfully submitted,

IVOR M. HUGHES

Ivor M. Hughes
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Agent for the Applicant

Marcelo K. Sarkis
Registration No. 37,015
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MKS*kdk
Enclosures
1. Petition for Extension of Time;
2. Check in the sum of $950.00 U.S.

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**PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)** | Docket Number (Optional) PT1817000

In re Application of Kenneth S. Albert et al.

Application Number 09/465,338 | Filed Dec. 17, 1999

For Chronotherapeutic Formulations of Diltiazem and the Administration Thereof

Art Unit 1615 | Examiner Amy E. Pulliam

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

- ☐ One month (37 CFR 1.17(a)(1)) $____
- ☐ Two months (37 CFR 1.17(a)(2)) $____
- ☒ Three months (37 CFR 1.17(a)(3)) $ 950.00
- ☐ Four months (37 CFR 1.17(a)(4)) $____
- ☐ Five months (37 CFR 1.17(a)(5)) $____

☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $____.

☒ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account Number 08-3255

I have enclosed a duplicate copy of this sheet.

I am the ☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 37,015

☐ attorney or agent under 37 CFR 1.34(a). Registration number if acting under 37 CFR 1.34(a) ____

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

February 3, 2004
Date

Signature

905-771-6414
Telephone Number

Marcelo K. Sarkis
Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☒ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*



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